



(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention  
of the grant of the patent:  
12.05.1999 Bulletin 1999/19

(51) Int. Cl.<sup>6</sup>: **A61K 31/23**, A61K 47/10,  
A61K 47/22, A61K 47/14,  
A61K 7/48

(21) Application number: **93110903.7**

(22) Date of filing: **08.07.1993**

(54) **Pharmaceutical compositions containing esters of omega-3 polyunsaturated acids and their use in the topical treatment of morbid affections**

Arzneimittel, die Ester omega-3 polyungesättigter Säuren enthalten und deren Verwendung in der topischen Behandlung morbider Erkrankungen

Compositions pharmaceutiques contenant des esters d'acides oméga-3 polyinsaturés et leur utilisation dans le traitement topique d'affections morbides

(84) Designated Contracting States:  
**AT BE CH DE DK ES FR GB IT LI LU PT SE**

(30) Priority: **11.08.1992 NL 9201438**

(43) Date of publication of application:  
**16.02.1994 Bulletin 1994/07**

(73) Proprietor: **PROSPA B.V.**  
**1017 Amsterdam (NL)**

(72) Inventors:  
• **Bruzzese, Tiberio**  
**I-20144 Milan (IT)**  
• **Mozzi, Giovanni**  
**I-20131 Milan (IT)**  
• **Ruggeri, Remo**  
**I-20090 Cinisello Balsamo, Milan (IT)**

(74) Representative:  
**Giambrocono, Alfonso, Dr. Ing. et al**  
**Ing. A. Giambrocono & C. S.r.l.**  
**Via Rosolino Pilo 19/B**  
**20129 Milano (IT)**

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## Description

[0001] The present invention relates to new pharmaceutical compositions containing esters of  $\omega$ -3 polyunsaturated acids and to their use in the topical treatment of morbid affections.

5 [0002] The treatment of morbid affections, in particular of psoriasis, phlebitis and the related pathologies is effected, since a long time, by orally administering formulations comprising  $\omega$ -3 polyunsaturated fatty acids or the esters thereof (usually the glyceride esters thereof) (Bittner S.B. et al., Lancet, 378, 1, 1988; Ziboh V.A., Arch. Dermatol., 122, 1277, 1986; Maurice P.D.L. et al., Brit. J. Dermatol., 117, 599, 1987; Woodcock B.F. et al., Brit. Med. J., 288, 592, 1984).

[0003] A number of collateral and undesired effects may be however present using systemic administering route.

10 [0004] On the other hand, topical compositions containing said  $\omega$ -3 polyunsaturated fatty acids or the esters thereof, have been, till now, never successfully prepared; in fact one of the main obstacles which has always prevented an effective topical use of said compounds and of their pharmaceutical formulations is their very unpleasant smell which derives from the oxidization, because of the atmospherical oxygen and of cutaneous enzymes, of the long chains thereof full of carbon to carbon double bonds which make up said  $\omega$ -3 polyunsaturated fatty acids.

15 [0005] Creams, lotions or gels containing esters of polyunsaturated fatty acids, which are initially odourless or pleasantly perfumed, assume, because of such phenomenon some hours after their application, a very unpleasant and repellent smell, which they confer decidedly to the skin whereon they have been applied to and to those clothes eventually put into contact therewith.

20 [0006] The use of perfumes or any other deodorizing agent, even if intense and strong, is useless. In fact, upon application of the cream or of any other topical form to the skin, the perfume volatile components evaporate faster than the higher boiling esters of polyunsaturated fatty acids, which assume, in a very short time, the above said very unpleasant smell.

[0007] The use of aloe extracts has been recently suggested for the deodorization of the oils having natural origins (Bockow B.I. et al., WO 91/16914), but even this artifice has revealed itself absolutely ineffective.

25 [0008] JP-A-3090022 and JP-A-30090046 disclose transdermal pharmaceuticals containing eicosapentaenoic acid or its esters for the treatment of skin diseases wherein a surfactant and an antioxidant, such as f.i. dibutylhydroxytoluene, are used.

[0009] The main purpose of the present invention is therefore to carry out a topical composition comprising esters of  $\omega$ -3 polyunsaturated fatty acids as the active ingredient which permit to attain positive results avoiding the collateral and undesired effects always connected to the systemic administration of drugs and avoiding the generation of very unpleasant and repellent smells which would make otherwise topical formulations useless.

30 [0010] It has been surprisingly found that the addition of phenolic antioxidants in suitable amounts to topical compositions of the esters of  $\omega$ -3 polyunsaturated fatty acids hinders the decomposition thereof and the generation of very unpleasant and repellent smells deriving therefrom.

35 [0011] In particular the present invention discloses a topical composition useful in the treatment of morbid affections comprising at least one  $C_1$ - $C_3$  alkyl ester of the cis- 5, 8, 11, 14, 17 eicosapentaenoic acid (EPA) and of the cis- 4, 7, 10, 13, 16, 19, docosahexaenoic acid (DHA) as the active ingredient, characterized in that it comprises at least one phenolic antioxidant, whose weight percentage, with respect to said at least one ester, ranges between 1.0 and 4.0 and that said at least one ester has a titer of at least 80% and a concentration from 25% to 40% w/w, and from 5% to 15% w/w of triethylcitrate with respect to said at least one ester.

40 [0012] It has been also surprisingly found that the addition of triethylcitrate to the compositions of the present invention magnifies the activity of said phenolic antioxidants in inhibiting and hindering the generation of very unpleasant and repellent smells.

45 [0013] The esters of  $\omega$ -3 polyunsaturated fatty acids suitable for the scope of the present invention are  $C_1$ - $C_3$  alkyl esters, preferably ethyl esters.

[0014] The phenolic antioxidants suitable for the scope of the present invention are selected among butylated hydroxytoluene, butylated hydroxyanisole and vitamin E; particularly suitable to the scope of the invention is the butylated hydroxyanisole.

[0015] Further, the phenolic antioxidants of the present invention are excellent deodorizing and stabilizing agents.

50 [0016] The pharmaceutical compositions which are the subject of the present invention are made dissolving the substances inhibiting and hindering the very unpleasant smells into the esters of  $\omega$ -3 polyunsaturated fatty acids (which appear as oily liquids) and subsequently englobing the mixture so obtained in the vehicle constituting the pharmaceutical form, according to the usual practice of pharmaceutical technology.

55 [0017] The topical compositions according to the present invention are active against psoriasis, phlebitis and atopic eczema.

[0018] To make clear the comprehension of the characteristics of the present invention, some embodiments will be hereinafter given by mere non limiting way of example.

**EXAMPLE 1**

[0019] A number of unpleasant smell inhibiting substances has been dissolved in the amounts set forth herebelow into an oily mixture of EPA and DHA ethylesters (overall titer > 80%).

5 [0020] Some filter paper strips have been impregnated with solutions thereof, exposed to air in different climatic conditions and then assayed through an olfactory test by a group of examiners.

[0021] In the following table, the results expressed with a score ranging between 1 (very unpleasant smell) and 3 (odourless or having a pleasant smell) have been reported.

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SMELL GENERATION AFTER AGEING OF THE EPA + DHA ETHYLESTERS ADMIXTURE									
COMPOSITION	INITIAL	EXPOSITION AT 45° AND IN THE DARK			EXPOSITION AT RT AND IN THE LIGHT				
		16 h	24 h	40 h	24 h	40h	64 h	88 h	150 h
EPA + DHA ethylesters mixture	3	1	1	1	1	1	1	1	1
+ 1% Vit. E	3	3	3	2	3	3	3	3	1
+ 1% A.P.	3	2	1	1	3	1	1	1	1
+ 1% BHA	3	3	3	3	3	3	2	3	3
+ 1% BHT	3	3	1	1	3	3	2	2	3
+ 10% TEC	3	1	1	1	1	1	2	1	1
+ 10% TEC + 1% BHT	3	3	3	1	3	3	3	2	3
A.P. = Ascorbyl palmitate BHA = Butylated Hydroxyanisole BHT = Butylated Hydroxytoluene TEC = Triethyl Citrate									

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**EXAMPLE 2 (Comparative)**

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[0022] Operating in a way analogous to that one described in the Example 1, a number of different amounts of butylated hydroxyanisole (BHA) and Vitamin E have been assayed.

40

SMELL GENERATION AFTER AGEING OF THE EPA + DHA ETHYLESTERS MIXTURE									
Composition	Initial	Exposition at 45° and in the dark			Exposition at RT and in the light				
		24 h	48 h	56 h	24 h	48 h	56 h	120 h	144 h
EPA + DHA ethylesters mixture	3	1	1	1	1	1	1	1	1
+ 0,03% BHA	3	1	1	1	3	3	3	1	1
+ 0,1% BHA	3	1	1	1	3	3	3	1	1
+ 0,5% BHA	3	3	2	1	3	3	3	3	3
+ 1% BHA	3	3	2	1	3	3	3	3	3
+ 3% BHA	3	3	3	3	3	3	3	3	3
+ 0,03% Vit. E	3	1	1	1	3	1	1	1	1
+ 0,1% Vit. E	3	1	1	1	3	1	1	1	1

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EP 0 582 834 B1

(continued)

SMELL GENERATION AFTER AGEING OF THE EPA + DHA ETHYLESTERS MIXTURE									
Composition	Initial	Exposition at 45° and in the dark			Exposition at RT and in the light				
		24 h	48 h	56 h	24 h	48 h	56 h	120 h	144 h
+ 0,5% Vit. E	3	2	1	1	3	2	3	1	1
+ 1% Vit. E	3	3	2	1	3	3	3	3	1
+ 3% Vit. E	3	3	3	3	3	3	3	3	3

EXAMPLE 3 (Comparative)

[0023]

EPA + DHA ethylesters mixture (overall titer > 80%)	g	30
Butyl hydroxyanisole	g	1
Mixture of saturated fatty acids glycerides and poly oxyethylenated saturated fatty acids	g	12
Carbopol 974P	g	0.3
Triethanolamine	g	0.3
Methyl p-hydroxybenzoate	g	0.12
Ethyl p-hydroxybenzoate	g	0.05
Propyl p-hydroxybenzoate	g	0.03
Perfume and depurated water q.s. to	g	100

[0024] Dissolve in the boiling water the p-hydroxybenzoates, thermostat at 75°C and dissolve Carbopol therein. Contemporaneously, melt at about 75°C the saturated fatty acids glycerides and polyoxyethylenated saturated fatty acids mixture and add, while stirring, the aqueous phase previously prepared.

[0025] Cool at about 60°C and add the EPA and DHA ethylesters mixture, wherein the butylated hydroxyanisole has been previously dissolved, to the emulsion. Add the triethanolamine to the so obtained mixture, cool at about 40°C, add the perfume and cool at room temperature.

EXAMPLE 4 (Comparative)

[0026]

EPA and DHA ethylesters mixture (overall titer > 80%)	g	30
Vitamin E	g	1
Mixture of saturated fatty acids glycerides and polyoxyethylenated saturated fatty acids	g	12
Carbopol 974 P	g	0.3
Triethanolamine	g	0.3
Methyl p-hydroxybenzoate	g	0.12
Ethyl p-hydroxybenzoate	g	0.05
Propyl p-hydroxybenzoate	g	0.03

(continued)

Perfume and depurated water	q.s. to	g	100
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- 5 [0027] Vitamin E is dissolved into the EPA and DHA ethylesters mixture before of the addition to the emulsion, the preparation of the present formulation being, for the rest, substantially analogous to that one of the Example 3.

Example 5

- 10 [0028]

15	EPA ethylester (titer > 80%)	g	10
	Blitylated hydroxy toluene	g	0.1
	Triethylcitrate	g	1
	Mixture of saturated fatty acids glycerides and polyoxyethylenated saturated fatty acids	g	6
20	Carbopol 974 P	g	0.5
	Triethanolamine	g	0.5
	Methyl p-hydroxybenzoate	g	0.12
	Ethyl p-hydroxybenzoate	g	0.05
25	Propyl p-hydroxybenzoate	g	0.03
	Perfume and depurated water q.s. to	g	100

- 30 [0029] The butylated hydroxyanisole and the triethylcitrate are dissolved into the EPA ethyl ester before of the addition to the emulsion, the preparation of the present formulation being, for the rest, substantially analogous to that one of the Example 3.

EXAMPLE 6 (Comparative)

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[0030]

40	DHA ethylester (titer > 80%)	g	40
	Butylated hydroxyanisole	g	2
	Mixture of saturated fatty acids glycerides and polyoxyethylenated saturated fatty acids	g	12
45	Carbopol 974P	g	0.3
	Triethanolamine	g	0.3
	Methyl p-hydroxybenzoate	g	0.12
	Ethyl p-hydroxybenzoate	g	0.05
50	Propyl p-hydroxybenzoate	g	0.03
	Perfume and depurated water q.s. to	g	100

- 55 [0031] The preparation is analogous to that one of the Example 3.

**EXAMPLE 7**

[0032] Using the procedures described in the foregoing examples, n.5 creams have been prepared having the following formulae:

		I (reference)	II (BHT)	III (TEC+BHT)	IV (A 1)	V (A 2)
10	EPA AND DHA ethylesters (overall titer > 80%)	g 30	30	30	30	30
	Butylated hydroxytoluene	g -	0,3	0,3	-	-
	Triethylcitrate	g -	-	3	-	-
15	Aloe powder	- -	-	-	2	-
	Aloe sol. 10 : 1	g -	-	-	-	15
20	Mixture of saturated fatty acids glycerides and polyoxyethylenated saturated fatty acids	g 12	12	12	12	12
	Carbopol 974P	g 0,3	0,3	0,3	0,3	0,3
	Triethanolamine	g 0,3	0,3	0,3	0,3	0,3
25	Methyl p-hydroxybenzoate	g 0,12	0,12	0,12	0,12	0,12
	Ethyl p-hydroxybenzoate	g 0,05	0,05	0,05	0,05	0,05
	Propyl p-hydroxybenzoate	g 0,03	0,03	0,03	0,03	0,03
	Perfume and depurated water	q.s. to 100 g				

[0033] Some filter paper strips, smeared with the various creams, have been exposed to the air in different climatic conditions and, then, assayed by an olfactory test by a group of examiners. The results expressed by a score ranging from 1 (very unpleasant smell) to 3 (odourless or having a pleasant smell) have been reported in the following table.

SMELL GENERATION AFTER AGEING OF THE CREAM					
Cream formula	Initial	Exposition at 45°C and in the dark		Exposition at RT and in the light	
		34 h	50 h	96 h	120 h
Control	3	1	1	1	1
BHT	3	2	1	3	3
TEC + BHT	3	3	3	3	3
A 1	3	1	1	-	-
A 2	3	1	1	-	-

**EXAMPLE 8 (Comparative)**

[0034] Using the usual procedures n.5 creams have been prepared having the following formulae:

		I (riferim.)	II (0,3% BHA)	III (1% BHA)	IV (0,3% Vit.E)	V (1% Vit.E)
5	EPA and DHA ethylesters mixture (overall titer > 80%)	g 30	30	30	30	30
	Butylated hydroxyanisole	g -	0,3	1	-	-
10	Vitamin E	g -	-	-	0,3	1
	Mixture of saturated fatty acids glycerides and polyoxyethylenated saturated fatty acids	g 12	12	12	12	12
15	Carbopol 974P	g 0,3	0,3	0,3	0,3	0,3
	Triethanolamine	g 0,3	0,3	0,3	0,3	0,3
	Methyl p-hydroxybenzoate	g 0,12	0,12	0,12	0,12	0,12
20	Ethyl p-hydroxybenzoate	g 0,05	0,05	0,05	0,05	0,05
	Propyl p-hydroxybenzoate	g 0,03	0,03	0,03	0,03	0,03
	Perfume and depurated water	q.s. to 100 g				

[0035] Some filter paper strips have been smeared with cream and assayed after exposition to the air, analogously to what has been done in the Example 7.

[0036] The results have been reported in the following table.

SMELL GENERATION AFTER AGEING OF THE CREAM							
Cream formula	Initial	Exposition a 75°C and in the dark	Exposition at 45°C and in the dark		Exposition at RT and in the light		
		6h	48h	72h	144 h	216 h	240 h
Control	3	1	2	1	1	1	1
0,3% BHA	3	3	2	2	3	3	3
1% BHA	3	3	3	3	3	3	3
0,3% Vit. E	3	3	2	2	3	1	1
1% Vit. E	3	2	3	3	2	3	3

#### EXAMPLE 9 (Comparative)

[0037] 8 patients afflicted with psoriasis, in various parts of their body, have been treated for four weeks with a cream containing a 30% mixture of EPA and DHA ethylesters (having an overall titer > 80%), having a formulation that is identical to that one of the Example 3

As to erythema and desquamation, a score ranging from 1 to 5 has been assigned to each patient at the beginning and at the end of the treatment.

A higher score corresponded to a greater seriousness of the symptoms.

The mean of the scores and the corresponding standard deviation thereof have been reported in the following table at the beginning and at the end of the treatment.

Treatment phase	Desquamation		Erythema	
	mean	s.d.	mean	s.d.
Beginning	3.1	0.64	3.4	0.74
End	1.9	0.99	2.0	0.93

[0038] The means obtained have been elaborated according to the t Student test and the respective decreases thereof, because of the treatment, have turned out to be highly significant ( $P < 0.01$ ) for what concerns either desquamation or erythema, thus confirming the effectiveness of the drug used.

#### EXAMPLE 10 (Comparative)

[0039] 6 patients afflicted with phlebitis have been treated for three weeks with a cream containing a 30% EPA and DHA ethylesters admixture (having an overall titer  $> 80\%$ ), having a formulation identical to that one of the Example 3.

[0040] The presence of ulcers and, by a score ranging from 0 to 3, the seriousness of the other components of the symptomatology: pain, oedema and cyanosis, have been registered for each patient at the beginning and at the end of the treatment.

[0041] A higher score corresponded to a greater seriousness of the symptoms.

[0042] The relevant results are reported in the following table:

Patient Nr.	Ulcer		Pain		Oedema		Cyanosis	
	begin.	end	begin.	end	begin.	end	begin.	end
1	YES	NO	2	0	2	0	3	1
2	NO	NO	3	1	2	1	3	2
3	YES	NO	3	1	3	1	2	0
4	YES	NO	2	0	2	0	2	0
5	YES	YES	3	2	2	1	3	1
6	NO	NO	2	0	2	0	2	0

[0043] The improvements attained because of the treatment which has been set up are evident.

#### Claims

1. A topical composition useful in the treatment of morbid affections comprising

- at least one  $C_1$ - $C_3$  alkyl ester of the cis- 5, 8, 11, 14, 17-eicosapentaenoic acid and of the cis- 4, 7, 10, 13, 16, 19-docosahexaenoic acid having a concentration ranging between 25 and 40% w/w and a titer of at least 80% as the active ingredient;
- at least one phenolic antioxidant, the weight percentage of which ranges between 1 and 4, with respect to said at least one ester; and
- from 5% to 15% w/w of triethylcitrate with respect to said at least one ester.

2. A topical composition according to claim 1, characterized in that said  $C_1$ - $C_3$  alkyl ester is an ethyl ester.

3. A topical composition according to any of the previous claims, characterized in that said at least one phenolic antioxidant is selected from the group consisting of butylated hydroxyanisole, butylated hydroxytoluene and vitamin E.

4. A topical composition according to claim 3, characterized in that said phenolic antioxidant is butylated hydroxy ani-



sole.

5. A topical composition according to any of the previous claims, characterized in that it is active against psoriasis.
- 5 6. A topical composition according to any of the previous claims, characterized in that it is active against phlebitis.
7. A topical composition according to any of the previous claims, characterized in that it is active against atopic eczema.
- 10 8. Use of the phenolic antioxidants of in a composition according to claim 3 as deodorizing agents.

#### Patentansprüche

1. Topische Zusammensetzung, die zur Behandlung morbider Affektionen geeignet ist, und folgendes umfasst:
  - 15 - mindestens einen C<sub>1</sub>-C<sub>3</sub>-Alkylester von cis-5, 8, 11, 14, 17-Eicosapentaensäure und cis-4, 7, 10, 13, 16, 19-Docosahexaensäure mit einer Konzentration im Bereich zwischen 25 und 40 % G/G und einem Titer von mindestens 80 % als aktiven Bestandteil;
  - 20 - mindestens ein phenolisches Antioxidationsmittel, dessen prozentualer Gewichtsanteil im Bereich zwischen 1 und 4 in bezug auf den mindestens einen Ester liegt, und
  - 5 bis 15 % G/G Triethylcitrat, bezogen auf den mindestens einen Ester.
- 25 2. Topische Zusammensetzung gemäß Anspruch 1, **dadurch gekennzeichnet**, dass der C<sub>1</sub>-C<sub>3</sub>-Alkylester ein Ethylester ist.
3. Topische Zusammensetzung gemäß mindestens einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet**, dass das mindestens eine phenolische Antioxidationsmittel ausgewählt ist aus butyliertem Hydroxyanisol, butyliertem Hydroxytoluol und Vitamin E.
- 30 4. Topische Zusammensetzung gemäß Anspruch 3, **dadurch gekennzeichnet**, dass das phenolische Antioxidationsmittel butyliertes Hydroxyanisol ist.
- 35 5. Topische Zusammensetzung gemäß mindestens einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet**, dass sie gegen Psoriasis aktiv ist.
6. Topische Zusammensetzung gemäß mindestens einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet**, dass sie gegen Phlebitis wirksam ist.
- 40 7. Topische Zusammensetzung gemäß mindestens einem der vorhergehenden Ansprüche, **dadurch gekennzeichnet**, dass sie gegen atopische Ekzeme wirksam ist.
8. Verwendung des phenolischen Antioxidationsmittels in einer Zusammensetzung gemäß Anspruch 3 als Deodorierungsmittel.
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#### Revendications

1. Composition topique pouvant être utilisée dans le traitement des affections morbides, comprenant
  - 50 - au moins un ester alkylique en C<sub>1</sub>-C<sub>3</sub> de l'acide cis-5, 8, 11, 14, 17-éicosapentaénoïque et de l'acide cis-4, 7, 10, 13, 16, 19-docosahexaénoïque, ayant une concentration comprise entre 20 et 40 % m/m, et un titre d'au moins 80 % en principe actif;
  - au moins un antioxygène phénolique, dont le pourcentage en poids est compris entre 1 et 4 par rapport au moins à un dit ester; et
  - 55 - de 5 à 15 % m/m de citrate de triéthyle, par rapport au moins à un dit ester.
2. Composition topique selon la revendication 1 caractérisée en ce que ledit ester alkylique en C<sub>1</sub>-C<sub>3</sub> est un ester

éthylque.

3. Composition topique selon l'une quelconque des revendications précédentes, caractérisée en ce qu'au moins un dit antioxygène phénolique est choisi dans le groupe comprenant l'hydroxyanisole butylé, l'hydroxy-toluène butylé et la vitamine E.
4. Composition topique selon la revendication 3, caractérisée en ce que ledit antioxygène phénolique est l'hydroxyanisole butylé.
5. Composition topique selon l'une quelconque des revendications précédentes, caractérisée en ce qu'elle est active contre le psoriasis.
6. Composition topique selon l'une quelconque des revendications précédentes, caractérisée en ce qu'elle est active contre la phlébite.
7. Composition topique selon l'une quelconque des revendications précédentes, caractérisée en ce qu'elle est active contre l'eczéma constitutionnel.
8. Utilisation des antioxygènes phénoliques dans une composition selon la revendication 3, en tant qu'agents désodorisants.